Determinants of therapy switch in multiple sclerosis treatment-naïve patients: A real-life study

DETERMINANTS OF THERAPY SWITCH IN MULTIPLE SCLEROSIS TREATMENT-NAÏVE PATIENTS: A REAL-LIFE STUDY

ABSTRACT

Background: With many options now available, first therapy choice is challenging in multiple sclerosis (MS), and depends mainly on neurologist and patient preferences.

Objectives: To identify prognostic factors for early switch after first therapy choice.

Methods: Newly diagnosed Relapsing-Remitting MS patients from 24 Italian centers were included. We evaluated the association of baseline demographics, clinical, and MRI data to the switch probability for lack of efficacy or intolerance/safety with a Multivariate Cox analysis and estimated switch rates by competing risks models.

Results: We enrolled 3025 patients. The overall switch frequency was 48% after 3 years. Switch risk for lack of efficacy was lower with fingolimod (HR=0.50;p=0.009), natalizumab (HR=0.13;p<0.001), dymethil-fumarate (HR=0.60;p=0.037), teriflunomide (HR=0.21;p=0.031) as compared to interferons. Younger age (HR= 0.96;p<0.001), diagnosis delay (HR=1.23;p=0.021), higher baseline EDSS (HR=1.17;p=0.001), and spinal cord lesions (HR=1.46;p=0.001) were independently associated to higher inefficacy switch rates. We found lower switch for intolerance/safety with glatiramer acetate (HR=0.61;p=0.001), fingolimod (HR=0.35; p=0.002) and dymethil-fumarate (HR=0.57;p=0.022) as compared to interferons, while it increased with

natalizumab (HR=1.43;p=0.022). Comorbidities were associated to intolerance switch (HR=1.28;p=0.047).

Conclusions: Several factors are associated to higher switch risk in patients starting a first-line therapy, and could be integrated in the decision-making process of first treatment choice.

Introduction

In recent years, therapeutic options for the relapsing remitting (RR) course of Multiple Sclerosis (RR-MS) have largely increased. The European Medicines Agency (EMA) and the Italian regulatory agency (AIFA)[1-2] have classified Disease Modifying Therapies (DMTs) as first- or second-line, according to the risk/benefit profile found in clinical trials.

Since there are no clear predictors of efficacy based on patients' baseline characteristics, first therapy choice depends mainly on personal attitude towards single DMTs, patients' preferences, and co-existing comorbidities[3-4]. Recently, new oral compounds have been licensed[5], making the choice even more complex.

For highly active RR-MS at onset of disease, with clinical and radiological signs of inflammation, second line therapies are also considered as first treatment choice. This category has enlarged with alemtuzumab[6] and more recently ocrelizumab[7], in addition to natalizumab and fingolimod. In more aggressive disease there are no clear indications regarding the first treatment choice, since real data comparisons deal with the oldest compounds, and mainly in patients switching from other therapies[8-14].

The scenario of RRMS treatment is also complicated by the high expectations that neurologists and patients have since the criteria of No Evidence of Disease Activity (NEDA) (absence of relapses, disability increase and disease activity on Magnetic Resonance Imaging (MRI)), have been introduced[15]. Patients with poor disease control are switched to different DMTs either with well-recognized higher efficacy or with different mechanism of action[16]. This attitude, however, has not been extensively analyzed in terms of efficiency, apart from single center reports[17-19]. Side effects may affect patients' tolerance and adherence[20-21], so that switches for side effects or poor tolerability are also very frequent[22].

There are still no established prognostic factors predicting persistence to a given therapy[23-24], so that real-life data can be helpful to identify clinical and demographic characteristics predicting early switch risk.

Aims of our study were i) to provide a snapshot of the prescribing attitude in newly diagnosed Italian MS patients from 2010 through 2017; ii) to describe the switch patterns from first therapy; iii) to define if baseline characteristics could predict patients' persistence on therapies, guiding first treatment choice.

Patients and methods

Study Design

We designed a multicenter, retrospective study, involving 24 Italian MS centers. The ethics committee of the coordinating center (Genova) approved the study. Raw data collection was approved by the local ethics committees at all centers. All the centers involved in the study ask for a written permission of use of anonymized personal clinical data for research purposes and written informed consent was obtained from all study patients included in this study. Inclusion criteria were: age over 16 years, diagnosis of RRMS (2001 International Panel Diagnostic Criteria and the 2010 revision)[25-26] and initiating a DMT between January 2010 and June 2017. There were no exclusion criteria.

We collected data using local databases that served as source data. Smaller centers reviewed patient's charts directly. We shared a common database template with predefined criteria for data categorization. All files were merged in one common database by a data manager (AS), and further processed for data cleaning, and analysis.

We collected demographics (age, gender, level of education) and clinical data at the time of diagnosis (baseline): date of disease onset and diagnosis, relapses in the previous year (excluding

relapses leading to diagnostic procedures), Expanded Disability Status Scale (EDSS), presence of comorbidities, presence of Gadolinum (Gd)-enhancing lesions, of more than 9 T2 lesions and of spinal cord lesions on the baseline MRI scan. Comorbidities classification was detailed in a previous paper[4].

First DMT, date of DMT initiation, date of switch to a new DMT and the new DMT, date of stop and re-start (if the patient re-started the same DMT), and date of last follow-up were recorded. To reduce data complexity, the reason for DMT switch/stop was grouped in two classes: lack of efficacy or intolerance/safety. Treating neurologist made the allocation in one of the two classes. Inefficacy was defined as the occurrence of at least one of the following: 3-month confirmed EDSS progression, relapse occurrence, radiological inefficacy (increase in T2 lesion load, presence of new T1-Gd enhancing lesions). MRI was collected at baseline and at treatment switch. Spinal cord MRI was not available during follow-up. Relapses were defined following clinical trial criteria: a change in the EDSS with an increase ≥ 0.5 points on the total score, or an increase of 1 point on two Functional Systems (FS) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS.

When possible, lack of efficacy was further classified as clinical (relapses, EDSS progression) or radiological (MRI lesions). If patients switched therapy for both clinical and radiological lack of efficacy, this was considered as lack of efficacy for clinical reasons. Intolerance/safety was broad including side effects, pregnancy and JCV positivity.

Reason for DMT switch/stop, EDSS, Relapses, MRI data, were all entered in local databases before data extraction and as part of clinical practice. Neurologists, expert in MS, were in charge of these procedures, and performed data extraction as well.

DMTs

We defined different treatment classes, grouping therapies together based on Italian prescription rules, as first- and second-line therapies. For some analyses we grouped Interferons in

one class (IFN); we grouped first-line therapies (IFN, GA, TERI, DMF), vs second line therapies (fingolimd and natalizumab) vs other. Also, first-line therapies were grouped as injectables (IFN and GA) with long follow up vs new orals (TERI and DMF), with shorter follow up due to their late approval. We defined a horizontal switch as a switch from one to another first-line therapy, and a vertical switch from first- to second-line therapy.

JCV antibody testing was performed as per good clinical practice in natalizumab treated patients, at least at therapy start and after 12 and 24 infusions, for PML risk stratification.

Data on neutralizing antibodies against IFN or natalizumab were not collected as not routinely performed in Italian MS centers.

Statistics

All statistical analyses were computed using code written in STATA (v.13; StataCorp). Survival analysis was used to generate Kaplan–Meier estimates for time to switch for any cause and a cumulative incidence analysis accounting for competing risks based on the model of Fine and Gray[27-28] was used to calculate the proportion of patients switching for poor efficacy vs intolerance and with an horizontal vs a vertical switch. Multivariate Cox regression, adjusted for center, year of diagnosis and age, was used to determine which baseline clinical, radiologic, and demographic features were related to the probability of switching therapy, with different models for switch due to lack of efficacy and due to intolerance.

Based on the factors emerging from the multivariate models, a baseline score was created to identify patients who start a first-line therapy at a higher risk for an early switch for poor efficacy. The sample was split 50:50 into a training and a validation set. All the analysis run on the training set were then validated on the independent set of data in the validation set. Calibration was performed by comparing the predicted probability of switch with the observed ones plotted as Kaplan-Meier curves according to the procedure recommended by Royston.[29] Harrell-C index was used to assess the discrimination ability of the model[30]. All the details about the prognostic factors

selection, model building, calibration and discrimination ability of the model are detailed in the Appendix. The predictive curves displayed were built on the validation set using the cumulative incidence accounting for competing risks based on the Fine and Gray model[28].

Results

Demographics

We screened 3025 patients; 2954 satisfied the inclusion criteria and were included in the analysis. Recruitment abilities varied among centers, ranging between 10 to 100% of all newly diagnosed patients, with a median of 40%.

Demographics and baseline clinical data are shown in **Table 1**. Follow-up duration had a median of 6.1 years (range 0.1-7.3) for patients with a diagnosis in 2010 and 0.13 years (range 0.-0.4) for patients with a diagnosis in 2017. Baseline brain MRI data were available for 87% of patients and spinal cord MRI for 77%.Among 750 patients (31.8%) with comorbidities, the more frequent were autoimmune diseases (n=176; 23.5%), followed by psychiatric (n=118; 15.7%), cardiovascular (n=109; 14.5%), neurologic (n=77; 10.2%) and metabolic (n=73; 9.7%).

Figure 1 shows the frequency of first therapy choice according to year of diagnosis. Baseline characteristics of patients according to their first therapy are reported in the supplementary material (**Table 1S**, supplemental material).

Figure 2 shows the overall switch frequency (15% after 1 year, 31% after 2 years and 48% after 3 years), divided into switch for lack of efficacy and switch for intolerance/safety (panel a) and into horizontal and vertical switch (panel b).

Switch for lack of efficacy

Multivariate associations between baseline demographic and clinical characteristics and the probability to switch for a perceived lack of efficacy are presented in **Table 2**. The switch frequency increased with year of diagnosis, with a risk of switch for lack of efficacy that is about 4-fold higher in 2016-2017 as compared to 2010-2011 (Table 2). Only licenced therapies were included in this analysis, excluding Alemtuzumab since the number of patients with this drug as

their first therapy was too low (n=18). Starting with IFN/GA as compared to oral therapies or a second line therapy (fingolimod or natalizumab) was the main factor associated to switch probability. The risk of switching (**Figure 3A**) for lack of efficacy is reduced by 50% starting with fingolimod (p=0.009) and by 87% starting with natalizumab (p<0.001) as compared to starting with IFN (IFN and GA have a similar risk of switch for lack of efficacy) and is reduced by 40% starting with DMF (p=0.037) and by 79% starting with TERI (p=0.031).

Among patients who switched for lack of efficacy (n=582), clinical reasons (relapses or progression of disability) were more frequent (n=365, 67%), as compared to radiological evidence of activity (n=182, 33%). For 35 patients (6%) who switched for lack of efficacy the reason for the perceived inefficacy was missing. Patients who switched for radiological activity had lower baseline EDSS than those who switched for clinical reasons (1.6 vs 2.1, p<0.001), and for them horizontal switch was more frequent than vertical switch (56% vs 32%; p<0.001). The opposite was true in patients who switched for clinical reasons (30% horizontal vs 60% vertical).

In order to extract practical guidelines from these results, we tried to identify those patients who started a first-line DMT grouped as IFN/GA (injectables) or DMF/TERI (new orals), and that were at a high risk of an early switch for lack of efficacy. Factors associated to a higher switch probability for lack of efficacy were estimated on the training set (50% of the sample) and the discrimination ability of the model was tested on the validation set (**Table 2S**, supplemental material). Factors associated to a higher switch probability were age at diagnosis, presence of spinal cord lesions on baseline MRI, a delay between onset and diagnosis and baseline EDSS (Harrel C =0.69 on the training and =0.64 on the validation set). Each patient was scored between 0 and 4 according to the presence of 0-1, 2, 3-4 factors associated to a higher risk of early switch (after grouping age at diagnosis as younger or older than 35 years (median value), delay between onset and diagnosis shorter or longer than 1 year (median value) and baseline EDSS as > or <= 2 (median value);**Table 3S**, supplemental material). After 2 years, 24% of patients in IFN/GA and 16% of

patients in DMF/TERI in the lower risk group (<=1 risk factors for switch) were estimated to change therapy for lack of efficacy; the percentage was, respectively, 45% for patients who started with IFN/GA and 30% for those who started DMF/TERI in the higher risk group (>3 risk factors for switch), (**Figure 4**).

Switch for intolerance/safety

Factors associated with intolerance/safety switch are reported in Table 2 (right panel). In this cohort, 16 patients (0.5% of the sample) switched due to reasons related to pregnancy. Different DMTs showed different switch probabilities due to intolerance/safety (p for heterogeneity<0.001). As shown in **Figure 3B**, patients treated with GA, DMF and fingolimod as their first therapy had the lowest probability to switch due to intolerance/safety. Taking IFN as the reference group the HR for GA was 0.61, (95% CI=0.46-0.81, p=0.001), 0.57 for DMF, (95%CI=0.35-0.92, p=0.022) and 0.35 for fingolimod (95% CI=0.19-0.68, p=0.002). Patients treated with natalizumab had a higher risk of switching for intolerance/safety (HR=1.43, 95% CI=1.05-1.94, p=0.022) with a clear switch frequency increase after 2 years (**Figure 3B**), mainly due to positivity to JCV antibodies test (49 out of 57, 86%). As previously reported[4], the presence of comorbidities at diagnosis was associated to intolerance switch (HR=1.28, p=0.047).

Discussion

We report the results from a large multicenter Italian observational study that enrolled newly diagnosed RR-MS patients from 2010 through 2017.

AIFA allows fingolimod and natalizumab prescription as first-line therapies in patients with high disease activity at baseline (i.e. two disabling relapses in the previous year and at least one T1 Gd-enhancing lesion or T2 lesion load increase in a recent MRI scan), limiting the prescription of both drugs for treatment naïve patients. The two new oral therapies, dimethylfumarate and teriflunomide, show profound difference with double as much dimethylfumarate use as compared to teriflunomide. It is possible that safety issue regarding the possible teriflunomide's teratogen effect may have limited its use in the females within this group of newly diagnosed MS patients, that are, for the vast majority, in the fertile age. A recent report has shown an unexpected safety of teriflunomide in women exposed to the drug during pregnancy[31], and may lead to a change in future prescription habits.

We found that the availability of new oral therapies reduced the number of patients treated with IFN. The effect was more evident for Interferon beta-1b, probably due to its more frequent administration, and troublesome adherence. The decrease of i.m. IFN beta-1a can be partly explained by the introduction of the pegylated version of this IFN. The use of GA remained stable over time, with a small increase in prescriptions in the last periods. Its different mechanism of action, tolerability profile ad use in patients with comorbidities may have played a role. Fingolimod was approved at the end of 2011, and its prescription rate increased progressively. Natalizumab use showed a small decline over time. Alemtuzumab was approved in Italy in 2015 and its use as a first therapy started to increase in 2016.

Overall, our study shows that poor efficacy is the predominant cause of switch from first-line therapy as compared to safety/intolerance. This indicates that the concerns raised by the probability of disability progression supersede those secondary to safety/intolerance. Alternatively, DMTs

currently in use in MS are overall well tolerated and side effects necessitating a therapeutic change are much more rare than clinical or radiological activity. Poor efficacy switch was more frequent in patients treated with first-line injectable therapies as compared to second-line treatments.

The first therapy being equal, younger age, reduced delay between onset and diagnosis, positive spinal MRI, and higher EDSS were all predictors of DMT switch due to poor efficacy. While the first three factors may indicate a more aggressive disease, higher EDSS as a predictive factor for poor efficacy switch may lead to different interpretations. Intuitively, a higher EDSS may be linked to a more aggressive disease, increasing the likelihood of switching for poor efficacy. A second possible explanation is that neurologists are more concerned about disease progression in patients with higher EDSS scores, as this may lead to irreversible disability, and are more willing to change therapy. This is confirmed by the higher prevalence of patients with higher EDSS and vertical (i.e. more effective) switches in those switching for clinical poor efficacy as compared to radiological poor efficacy. The higher prevalence of horizontal switches in patients with radiological poor efficacy supports this theory, as this may be translated into a search for a new mechanism of action rather than an increase in overall efficacy.

Using baseline factors to identify high-risk patients proved to be useful as it correctly identified subjects with a high switch propensity. Results showed that INF/GA patients with at least 3 of the 4 defined risk factors for poor efficacy switch (younger age, higher EDSS, presence of spinal cord lesions, shorter delay between onset and diagnosis) are at a higher risk (>30%) to switch for poor efficacy within 2 years. A validation on an external dataset would be warranted to generalize the prediction ability of the proposed model. We could speculate that treating high-risk patients with second line DMTs as a first choice may help reduce poor efficacy switches and possibly have a better control on disease progression. In more recent years, switch tendency increased, and this may be the result of a larger therapeutic repertoire, thus encouraging earlier DMT switch for perceived incomplete efficacy.

As for intolerance/safety switch, the choice of first treatment played a different role in DMT switch. GA and fingolimod showed the best persistence on treatment. This is supported by the safety/tolerance profile of both DMTs. Natalizumab had very few switches until the two-year cut point when the majority of patients were switched to other drugs, mainly because of positive anti-JCV antibodies. We are aware that the high number of intolerance/safety switches in the natalizumab group may have masked a discrete number of inefficacy switches leading to its underestimation. New oral drugs showed tolerability comparable to injectable first-line drugs with a lower rate of switch for lack of efficacy.

Our study suffers from some limitations, such as the observational and retrospective nature of the design, accounting for possible differences in data collection across centers. However, all the patients at their first therapy, included in this large cohort study, were enrolled in highly specialized Italian MS centers.

In contrast to our results, recent papers pointing at the persistence on injectable or oral first line therapies[32-33], showed that, in the short term, poor tolerance was the main determinant of therapy switch. These studies, however, had different inclusion criteria, considering patients with previous DMT history and excluding patients escalating to a second line therapy. In contrast, our study was focused on treatment-naïve patients and evaluated all possible causes for treatment switch.

In conclusions, our data showed that almost half of patients had their first treatment changed, mainly for poor efficacy, after 3 years from treatment start. We also show that identification of high-risk patients may be helpful in first treatment choice so to concentrate available resources in patient follow-up. The advent of new oral therapies and new monoclonal antibodies will hopefully improve DMT efficacy and patients persistence.

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Author contributions

FS acquired the data, participated in data analysis and interpretation, wrote the manuscript draft.

RL acquired the data, participated in data analysis and interpretation, wrote the manuscript draft.

AS managed, analyzed and interpreted the data and wrote the manuscript draft.

GTM, PA, DB, LP, EB, SL, AR, MC, SB, SL, SR, AL, JF, EC, VT, IRZ, AS, ES, SR, CC, RC, SP, AD, LL, CB, CVR, BF, SE, DI, FG acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.

MPS analyzed and interpreted the data, wrote the manuscript draft and supervised the study.

Potential Conflict of Interest

Francesco Saccà received personal compensation from Novartis, Almirall, Genzyme, Biogen, Merck Serono Forward Pharma and TEVA for public speaking, editorial work and advisory boards.

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Pietro Annovazzi served as advisor and received speaking honoraria from Novartis, Merck Serono, Genzyme, Biogen and Teva Italia.

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